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THE HUMAN THERMOREGULATORY SYSTEM: REGULATED SYSTEM OR SERVO SYSTEM?

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16. Abstract

Control theory is used to construct a model of the human thermoregulatory system to determine the nature of the mechanism which keeps the body at a relatively constant temperature. Findings seem to negate the set-point theory, indicating that, rather than returning its central temperature to a set point, the body instead seeks to return its instantaneous heat storage rate to zero. The system is therefore a servo system.

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INTRODUCTION

The body possesses regulatory mechanisms to keep the various /A311 elements of the internal environment constant. For a long time, physical regulatory mechanisms have been studied from a purely biological and descriptive point of view. However, a special branch has developed in the technical field during the past few years which deals specifically with the problems of regulation: the science of regulatory and control systems, or "control theory." There can be no doubt that physiology will benefit from the methodology and tools -- primarily mathematical ones -- which have been developed to meet the needs of control theory -- or rather, for which this field has found new uses. Biological phenomena are extremely complex, of course, and this complexity does in fact constitute one of the limitations of the application of control theory to physiological mechanisms. Moreover, in biology the phenomenon to be analyzed presents itself to us just as it is, while control theory usually proceeds in the reverse manner, constructing complex regulatory systems from simple structures. Nevertheless, to discuss the value of control theory in the analysis of biological problems is to overlook the fact that a rational simplification of these problems is sometimes necessary, and also that any biological problem is ultimately based on purely physical and chemical data. Finally, the use of a science of this type is bound to provide a stimulus for physiological research, due to the new lines of approach it provides for given problems and because it requires the translation of the problem into precise terms: definition of directly and indirectly regulated parameters, /A312 definition of control mechanisms, etc.

With its methodological aspect, control theory also furnishes some new tools. Since "modeling" and the establishment of

*Numbers in the margin indicate pagination in the foreign text.

models are not specific to control theory, as a result the term "model," which is widely used in physiology, has become extremely ambiguous in this usage (cf. Hardy [26]). Thus there are no common measurements between an "anatomic" model of arterial blood pressure regulation, including baroreceptors, bulb, heart, vessels, and the arrows connecting them, and an analog model of the same regulatory system, permitting simulation of the physiological processes and possible prediction of the behavior of the system in response to a given perturbation.

II. THEORETICAL ANALYSIS

Representation by analog model is often used productively in thermoregulatory analysis. The existence of an analogy between the law of heat flo (Fourrier's law) and the law of flow of electricity (Ohm's law) provides the basis for the main models developed in this discipline [18, 63, 71]. Nevertheless, by their very nature these models specifically describe heat exchanges and the role of various physical parameters (central temperature, skin temperature, etc.) in the significance of these exchanges. They provide less information on the internal regulatory mechanism. An everyday example will clearly illustrate this problem. Let us assume a simple thermostat-controlled bath. This bath may be subjected to various perturbations tending to displace the temperature equilibrium. If a number of quantitative results on the experimental findings in regard to the perturbation are available, it becomes possible to describe the manner in which the equilibrium temperature will be re-established by using mathematical heat exchange equations allowing for the various parameters involved. On this basis, the construction of an analog model will permit the simulation of exchanges and the prediction of thermal variations. However, at no time does this type of model require any assumptions as to the mechanics of operation of the thermostat itself.

On the other hand, it is possible to set up another type of model whose purpose is to describe the internal operation of the control system which keeps the temperature of the thermostat-controlled bath constant despite the perturbations. This might be an "all-or-nothing temperature regulator," for example. This would therefore be a model in the sense in which the term is used in control theory. This type of model and the method of reasoning used in its design are not very widely used in thermoregulation in comparison to other methods; thus they are not mentioned in the Hardy article [26]. One may wonder, however, whether the study of physical regulatory /A313 systems does not constitute a technical gap, since it does not make use of the methods which should be used in control theory in a similar problem.

The purpose here is to apply the methodology of control theory to the study of human thermoregulation and, on this basis, to show that the most widely held theory on the internal operation of the thermal controller," that of the central thermostat, is not the only possible assumption.

However, before even considering this theory, we feel it necessary to review the manner in which the problem of regulation is presented in control theory (cf. the work of Milhorn [42] and that of Gille, Decaulne and Pelegrin [21]).

A. Automatic Control Systems

The simplest diagram for a control system is that combining the input and output of the system by a relationship which will be termed the "transfer function," and which will be represented as F(s):

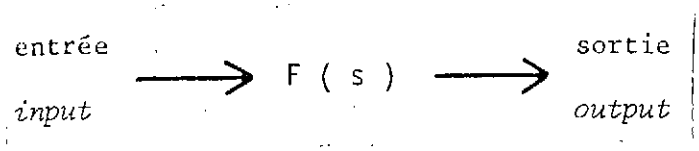

Fig. 1: Diagram of an open-loop control system.

This type of control system is an "open loop" system. It may match the calibration of a thermometer, for example; the input is the real temperature, the output the temperature

read and F(s) the relationship dealing with the characteristics of the thermometer.

If one wishes to keep the output at a given value, however, the control system must be informed of the output value. In this case we have a "closed loop" system. In the previous example of the thermostat-controlled bath, the real temperature of the bath is compared to a previously fixed set-point, and the system operates in such a way that the real temperature is as close as possible to the set temperature. For this purpose, the real temperature is compared with the set temperature by a "comparator."[1] The difference between the two, the "error" or "error signal," generally represented/A314 by ε, will trigger corrective heating or cooling mechanisms (Fig. 2).

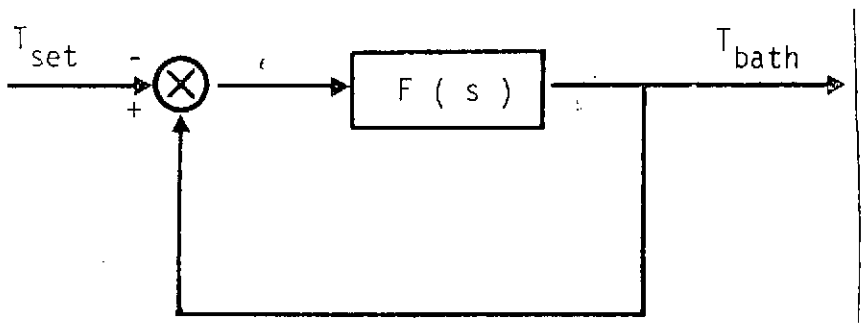

Fig. 2: Diagram of a temperature regulation system (thermostat-controlled bath).

Here F(s) is a global relationship. In the example chosen, it covers the characteristics of the thermostat itself, but also a number of other parameters: weight of water, thermal insulation of bath, etc. This is an important point which explains the apparent simplicity which these models sometimes seem to have at first glance. It is true that in the diagram the regulatory system (thermostat and detectors) can be separated from the "passive," regulated system (tank, water, and their thermal properties). On a theoretical level, however, it is not always possible to determine the transfer function.

1. The phraseology here is not always consistent, but the term "comparator" is the one which is most frequently used by control theory specialists, at least in France.

Finally, this basic model will be complicated by the existence of perturbations which may affect a given point in the system.

Two methods of regulation are conventionally described: the regulated systems per se, and the follow-up systems. However, this difference is not fundamentally absolute, and in some cases the behavior of a given system may differ depending on the analytic approach.

1. In a regulated system per se, one attempts to keep the output constant and as close as possible to the set-point, which here serves as an input parameter, despite the existence of perturbations. The thermostat-controlled bath is the most characteristic example of the regulated system per se, with the regulated parameter obviously being the temperature of the bath.

2. In a follow-up system, the input varies constantly, and the purpose of this system is to keep the output as close to the input as possible, that is, to "follow" the variations in the input in such a way that the error is constantly returned to zero despite the existence of perturbations. The classical example of this type of system in control theory is that of tracking radar, which must follow the target no matter what maneuvers it may perform. The motion of the eye fixed on a moving object is a physiological example.

B. Thermoregulation: the Theory of a Central Thermostat

One theory is by far the most widely used to explain in the operation of the thermoregulatory system: that of a "central thermostat." Set forth for the first time by Liebermeister [54], it has subsequently been developed in great detail to adapt it to the experimental findings which have gradually been obtained. In its simplest mode of expression, it is based on the assumption that the central temperature of the body, T_{de} (deep body temperature) is the regulatory parameter of the system. This implies that the control system has a reference value which is the equivalent of a temperature

T_{set} (set-point). The difference between T_{de} and T_{set} is the error signal which triggers the heat- or cold-combating mechanisms. It will immediately be seen that, independent of any assumptions, the perturbations which affect the body are not symmetrical. A "cold" perturbation can come only from the outside, with the exception of experimental manipulations or specific cases; this is a "negative" thermal load imposed on the body by the ambient conditions. A "hot" perturbation may arise either from inside the organism (internal load H_{int}) or from outside (external load H_{ext}) when the ambient temperature is higher than that of the body. Due to the very nature of metabolism, there is always an internal load whose value at least corresponds to the basal metabolism, but which may increase considerably during muscular exercise.

No matter what the perturbation may be, the most elemtary diagram for the regulation of T_{de} by central thermostat may be set up as given in Fig. 3.

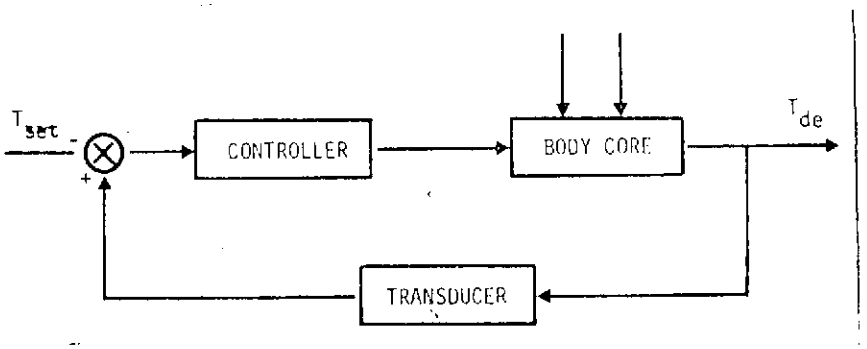

Fig. 3: Diagram of deep body temperature regulation by thermostat in its simplest form.

Everyone recognizes the inadequacy of a model of this type. It raises several problems, the first of which is that the deep body temperature varies, within limits which are relatively narrow, of /A316 course, but which cannot be explained by inaccuracies in the heat monitor. This point is of prime importance. To overlook it, as some investigators do (cf. [37], for example) means to neglect one of the essential phenomena involved in regulatory mechanisms. The level

T_{de} in a steady state varies in response to a number of factors which may be arbitrarily divided into two groups: factors which are directly thermal and which are not directly thermal in origin.

Factors which are directly thermal in origin: variations in the thermal load of the body entrain changes in the level of T_{de}, obviously excluding the possibility of any overriding of the regulatory mechanism. Thus it has been known for some time that [48] that an increase in the internal load by muscular exercise will result in an increase of T_{de} in a steady state. This finding has had ample confirmation [58, 56, 47]. In the subject at rest, whose internal thermal load is therefore slight, there is a relationship between T_{de} and the external thermal load, -- the ambient temperature, generally, that is [17, 15, 30, 20], -- provided that a steady state is reached, of course. In this case, in an initial phase the change in thermal load provokes a change in skin temperature T_{sk}, which draws attention to the role of cutaneous thermoreceptors. These various points, which are extremely important, will be discussed in more detail later on.

Factors which are not directly thermal in origin: these are quite numerous. Along these lines one might mention the thermal changes observed during the estrous cycle, or more simply, nychthemeral variations, which are known to persist in the absence of any physical activity, or in other words, any change in internal thermal load. A final example is provided by the thermal changes occurring during paradoxical sleep [39, 3, 50].

The model of the central thermostat must be made more complex to take these phenomena into account. In attempts to increase the conformity of the model with experimental data, one attractive theory is to assume that these various factors are capable of affecting one of the most characteristic elements of the system, T_{set} in the present case. As soon as one makes the complementary assumption that the set-point temperature may vary in response to various

factors, one of the flagrant inadequacies of the model begins to appear. This assumption provides the basis for the theory proposed by Hammel et al. [24]. The possible variation of the set-point of a regulator is a classical phenomenon in control theory, and this conceptualization is completely plausible as a result. It allows for a directly comprehensible explanation of the physiopathologic phenomena of thermal disorders. Thus according to this conceptualization, the phenomenon of fever would be nothing more than a resetting.

Nevertheless this theory is subject to some criticism. In /A317 regard to the classical case of the increase in T_{de} during muscular exercise, Benzinger [4] has pointed out that there is no information on how muscular activity is able to affect the T_{set}, i.e. whether this is by chemical or nervous action. He has proposed an explanation which does not draw on a set-point variation of this type. During muscular exercise, the increase in thermal load results in an increase in sweat secretion as a corrective mechanism. The evaporation of sweat cools the skin, thus decreasing the T_{sk}. This phenomenon would have a tendency to inhibit sweating, resulting in a secondary increase in deep body temperature. According to this investigator, therefore, "The antihomestatic inhibition of sweating explains the rise in central temperature" (ibid, p. 715). According to this concept, one can see that cutaneous cooling may occur without any change in T_{set} and that this phenomenon occurs through cutaneous thermoreceptors, whose extremely important role will be considered later on, or that it may directly affect the sweat gland. The idea of a change in the characteristics of the cutaneous effector is a theory which is currently upheld by some investigators [19, 44, 45, 65]. In this case, all the phenomena involved would occur as if, for a given order arising from the regulatory centers, the flow rate of the sweat gland and the evaporation of the sweat produced would vary with the temperature of the skin itself.

There are other possible reservations which are not specifically concerned with the theory of a variable set-point temperature, but

which deal more basically with the theory that there is a precise regulated temperature within the body. These reservations arise from two groups of findings: (1) certain problems in explaining easily observed biological phenomena, and (2) methodological inadequacies. A study of the latter group will serve as an introduction to a discussion of the method we have used. The first group of findings will be discussed below.

Is there a precise organ whose temperature is directly regulated? Deep body temperature is only a convenient concept, not a physical reality. There are as many "central" temperatures as there are points of measurement. One need only review discussions on the value of a given temperature as representative of T_{de}: rectal, esophageal, tympanic, and hypothalamic temperatures, etc. Nevertheless the hypothalamic temperature (T_{hypo}) generally seems to be considered the regulated temperature.

However, the temperature of a given body structure depends on several parameters, including on the one hand the quantity of heat brought to the structure by the blood, which in turns depend on the temperature of the arterial blood and the local blood flow rate, and thus on vasomotricity, and on the other hand, the heat output and thermal insulation of the structure involved. As a result, the assumption that the temperature of a given organ is regulated implies that the regulation affects all these factors, with the exception of those which can be shown to remain constant, and also /A318 that this regulation must be perfectly coordinated. There is virtually no information on this point in the literature.

In addition, in regard to the hypothalamus itself, we know that this is not the only organ which triggers thermoregulatory mechanisms when when it undergoes a change in temperature. These mechanisms may be triggered by the thermal stimulation of a number of structures in the central nervous system: the spinal cord [60, 23, etc.], the mesencephalon [41], etc. These regulatory-type actions produce a variation in the "central temperature" of the body, and also

a variation in T_{hypo} as a result. If this last parameter were regulated directly, there should be a rapid secondary inhibition of the previously triggered functions, and this is not observed. For example, cooling of the spinal canal produces an increase in O_2 consumption, in rectal temperature and in diencephalic temperature, without any apparent inhibition of the increase in T_{hypo} after 40 minutes of cooling [60, page 218]. One may of course object that the variations in T_{hypo} remain below preceptible levels. Since these variations are several tenths of a degree C, it must therefore be assumed that the sensitivity of the hypothalamic structures is fairly low, taking the quality of the thermoregulation into account. Moreover, continuous recording of T_{hypo} [1, 53] and other regions of the central nervous system -- the cerebellum, for example [68] -- show that these vary spontaneously.

Furthermore, thermoregulatory responses may be triggered by the thermal stimulation of receptors located outside the central nervous system, primarily in the skin. The work of Richet [54] has shown that thermal polypnea may be triggered in the dog by an increase in temperature, either on the skin on within the body (inhalation of warm air). This is the classical dichotomy between reflex polypnea and central ploypnea. It also arises in regard to cold in the form of the reflex shiver vs. the central shiver. The problem has been expanded on by Chatonnet and Tanche [9, 10], who have shown in a precise manner that the central temperature at which shivering occurs, for example, is lower as the skin temperature becomes higher, and vice versa. Currently it is widely assumed that variations in T_{sk} are capable of triggering regulatory action, and that at lease some of the cutaneous thermal detectors play a definite, but obviously not exclusive, role in thermoregulation [9, 10, 27, 51, 12, 13, 8, 25, 44]. Variations of this type occur when the body is subjected to heat or cold, that is, a positive or negative external thermal load.

On the other hand, when the body is subjected to an increase in internal load such as that produced by muscular exercise, the

muscular temperature is the first to increase. In this case it is possible to show a relationship between muscular temperature and the rate of evaporation $\dot{E}$ [48, 56, 57], although it is not possible to /A319 determine the nature of the receptors involved: the receptors of the central nervous system, or hypothetical intramuscular or vascular thermoreceptors. Finally, it should be recalled that thermoregulatory-type responses can be obtained, at least in some species, by heating the abdominal cavity [52].

It therefore becomes obvious that it not enough for an organ to be thermosensitive, i.e., for it to trigger thermoregulatory effects when it is thermally stimulated, to ensure that the temperature of this organ is directly regulated. If this assumption is made for a given organ, the hypothalamus, for example, it must also be assumed that all thermosensitive structures have their own temperature regulatory mechanisms.

C. Proposed Hypothesis

As soon as one sets aside the preliminary assumption that there is "one" temperature whose regulation appears to be preferred, it is possible to shift the focus of the problem. Now, regulatory effects may be obtained equally from hypothalamic, medullar and cutaneous signals, etc.; as a result, one ought to assume that these signals, if integrated by the monitor according to a given weighting, furnish the monitor with information as to the "mean temperature" of the body at a given time t, or rather, the level of the overall thermal state, since there is an extremely precise relationship between quantity of heat ΔQ, mass m, specific heat C, and temperature difference ΔT:

$$\Delta Q = m \cdot C \cdot \Delta T \qquad (1)$$

Obviously it is impossible to determine the absolute quantity of heat of the body, but its variations can be obtained. When the body changes from a steady state I to a steady state II, e.g., from an ambient temperature of 30° C to an ambient temperature of 40° C, the various temperatures of the body, primarily T_{de} and T_{sk},

are found to have increased. This represents an increase in the quantity of the heat of the body. From a neurophysiological standpoint, it additionally represents a quantitative and qualitative change in the signals reaching the heat monitor. Despite its arbitrary and abstract nature, the concept of mean body temperature (T_b) reveals the above phenomenon, that is, the relationship between thermal load, evaporation response and T_b in a steady state [14, 61]. An idea which is quite similar, although formulated differently, has been developed with greater precision by Nadel, et al. [44], who has shown the sweat rate to depend on the summation of T_{de} and T_{sk}. The convergence of the signals transmitted from the skin to /A320 the diencephalon and the mesencephalon has been clearly demonstrated by several reports [6, 28, 70, 46, 49, 72].

This theory may be carried still farther. If the body is regulated on the basis of the weighted sum of the information generated by all the thermoreceptors, then the regulatory signal corresponds to a change in the thermal level of the body. This is the reverse of the usual premises, which state that the central temperature of the body is regulated by the modification of exchanges. On the contrary, the body can be said to regulate its exchanges first in such a way that the algebraic sum of the fluxes occurring in heat gain and heat loss remains as close to zero as possible. As a result, the variations in the different body temperatures, especially the central temperatures, remain within a narrow range.

In the form of the classical heat exchange equation, this amounts to the statement that the algebraic sum of the thermal fluxes corresponding to the metabolic output dM/dt and to exchanges with the environment by convection, conduction, radiation and evaporation, represented by dC/dt, dK/dt dR/dt and dE/dt, respectively, should remain zero. If this is not the case, the body is storing heat or cold, or in algebraic terms, dS/dt. This equality may be simplified

typographically by writing:[2]

$$\dot{M} + \dot{C} + \dot{K} + \dot{R} - \dot{E} = \dot{S}$$

As a result, in the theory presented here, the process occurs as if c' were the value $\dot{S}$ which the controller must regulate so that it remains zero. It should be emphasized here that this is not a question of heat storage, represented by S, but of its derivative over time.[3] Of course the body can be informed of the value of $\dot{S}$ and/or its integral only by thermal stimulation of all its receptors. In this regard, the theory given here is quite close to /A321 that of investigators who consider the various temperatures, central and cutaneous to operate by summation.

This regulatory concept is not a new one. It has been clearly expressed by Glaser and Newling [22]. We have been noticing it in various publications for several years now [31, 32, 59, 34, 55, 36]. In parallel with our work, Snellen [62] has furnished a concise

[2] In our opinion, the above notation, which has been proposed if not used in thermoregulation analysis, is insufficient and ambiguous. It fails to make the distinction, an elementary one from a mathematical standpoint, between a quantity of heat (or quantity of sweat) and a heat flux (or sweat rate), the latter being a derivative of the former with respect to time. According to this code, the symbol E represents heat flux. But is this actually a flux? A number of articles seem to indicate that this is not the case. Even if it is, however, the question of how to express a quantity of heat lost by evaporation remains. Here one might make use of the analogy with the notation used in respiratory physiology. In this field a justifiable distinction is made between a real, instantaneously characterized flow rate V and a volume, even one measured over a given time, $\dot{V}_t$, for example. By analogy with this notation, we are using a dotted letter, $\dot{E}$, for example, to express a real, "instantaneous" flux, the international unit being the watt, and the letter E to express its integral, i.e., a quantity of heat, the unit in this case being the joule, which is preferred to the kilocalorie.

The ambiguity arises from the fact that a quantity of heat is generally determined over a given time (integral between t_2 and t_1) and is expressed in joule/minute or joule/hour.

However, this ambiguity has not escaped the attention of other investigators, who, although their notation again is sometimes ambiguous, do represent the real sweat rate by a dotted letter, $\dot{m}_{sw}$ in the present case [64].

[3] See page 11.

expression for this problem in the phrase: "temperature regulation or heat regulation?"

III. GENERAL METHODOLOGY

Before expanding on this theory, however, we would like to stress the methodology. We have pointed out that the characteristic methodology for study of the regulatory system has seldom been used in the study of thermoregulation. Now, it appears that certain conceptual errors are frequently made due to methodological error. These may be grouped under two headings:

1) The fact that a relation between parameters is found does not in any case imply a cause-and-effect relationship. This fact, which is universally acknowledged, does not always seem to be kept in mind in practice. Thus finding a relationship between $\dot{E}$ on the one hand and T_{hypo} and/or T_{sk} on the other does not necessarily mean that the hypothalamic temperature is the factor determining the sweat rate. This merely indicates that there is some probability that these parameters are related. Moreover, since T_{hypo} partly depends on variations in the quantity of heat of the body and since $\dot{E}$ is one of these factors, the existence of a relationship between T_{hypo} and $\dot{E}$ would seem to be eminently probable from a physical standpoint.

2) The lack of systematic use of the methodology of regulation study results in the neglect of several highly important parameters, such as time, for example, and the physical phenomena related to it, such as the time constant of the various regulatory responses. This also leads to a certain ambiguity in the terms used. For example, the terms "steady state" and "transient" are understood in a general sense which is sometimes quite remote from their specific meaning in control theory.

Thus "the steady input of the system is the term applied to an input e(t) whose expression as a function of time is constant, is a linear or parabolic function, or is a periodic function. When the expression of the output of the system as a function of time is

of the same type as that of the input (constant, linear or parabolic, periodic), the system will be termed "steady state." During the time the system takes to change from steady state I to steady state II, it is in a transient state" [21].

Thus the term "transient" should be reserved for a precise /A322
state of the system, rather than a given variation of the input. Moreover, a system may be in steady state but still correspond to a lack of "balance" on a physiological level. Thus during a linear increase in ambient temperature. T_{de} increases linearly [33]: physically speaking the system is in a steady state, while biologically, it is progressing inevitably toward hyperthermia.

To study a regulated control system, it is classical procedure in control theory to subject the input of the system e(t) to a known perturbation and to study the output s(t). Setting aside the "pulse" perturbation, the types of changes which e(t) may undergo are as follows:

a) Step input: steady state I is defined by the expression $e(t) = 0$, and steady state II by the expression $e(t) = 1$. There is discontinuity between the two.

b) Ramp input: steady state I is defined by $e(t) = 0$, and steady state II by $e(t) = at$.

c) Periodic input: steady state I is defined by $e(t) =$ constant, and steady state II by a periodic variation such that $e(t) = \sin \omega t$.

IV. EXPERIMENTAL BASIS

With Colin, we have expanded the study of human thermoregulation, primarily in the hot zone, by using control theory methodology. The following perturbations were applied: step input [12, 15], obtained by a theoretically instantaneous increase in external thermal load (generally an increase in ambient temperature T_a); ramp input by an increase in the radiant temperature, following a

linear relationship over time [33]; and finally, at present we are having subjects undergo a sinusoidal variation in external thermal load (radiant temperature). Preliminary results have recently been reported [40].

The heat balance was always established in continuous or subcontinuous fashion (one sample/min) on the basis of various environmental parameters (temperature, humidity, air speed) and physiological parameters (T_{de}, T_{sk}, $\dot{E}$ or, if this was not available, M, etc.).

RESULTS

Taking the various tests performed into consideration, the results which lent themselves best to schematic representation were those obtained with step input. In this case, steady state I, which will frequently be termed the "starting level" in the following discussion, is that of the nude subject at rest in a given /A323
environment. Generally, the environment is one of "neutrality," defined by the environmental parameters: temperature (T_a), humidity (P_{wa}), and relative air speed (V), such that T_a = 30°C, P_{wa} is less than 10 mm Hg, and V is less than 1 m/sec. These parameters define an overall thermal load H_1 (negative in this case). This steady state I can be reached only after 60-90 minutes of exposure. Only after a time lapse of this sort can one be sure of obtaining "neutrality" due to the lack of involvement of corrective mechanisms against heat (sweating) and cold (increase in $\dot{M}$).

The step increase in T_a at time t_0, corresponding to a new thermal load H_2, produces phenomena which may be described in three successive phases (Fig. 4):

Phase 1: T_{sk} rises very quickly; T_{de} remains roughly constant. $\dot{E}$ remains at its previous level, that is, $\dot{E}_1$. Thus there is a delay in the triggering of the central corrective mechanism, sweating. This phenomenon, which has been pointed out by Adolph [2], /A324
has not always been given the attention it deserves. It is of

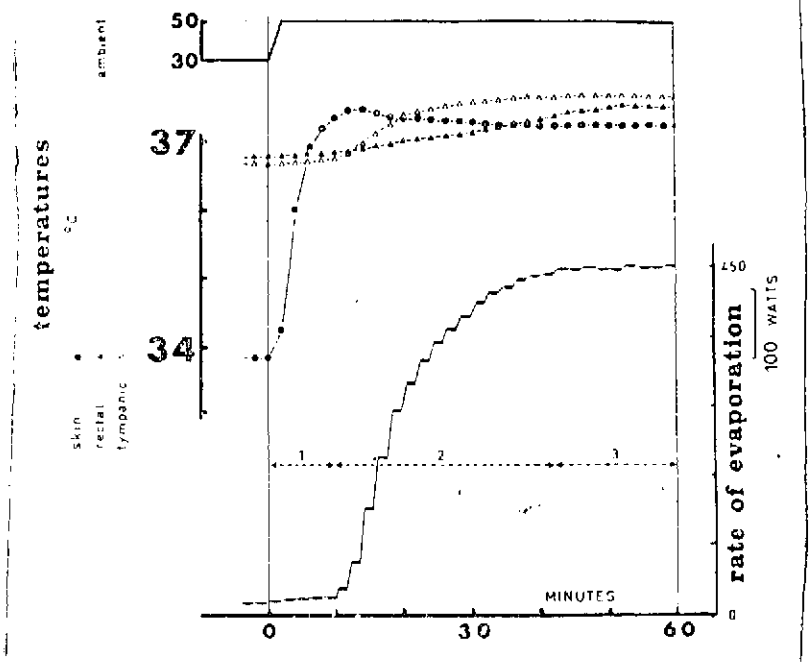

Fig. 4: Evolution of physiological thermal parameters (central temperature -- here rectal or tympanic, -- average skin temperature, rate of evaporation) during a step increase in ambient temperature (cf. text).

prime importance, nevertheless, since it corresponds to a transient state of the system in the true sense of the word. It is obvious that the delay consists of several phenomena of a peripheral nature: the thermal "inertia" of the body, vasomotor changes with a short time constant [38], followed by the secretion of sweat, excretion along the sweat canal, partial diffusion within the superficial cutaneous layer, and the beginning of true evaporation. Since the time constant of these latter phenomena is short, however, [8,45], the delay appears to be primarily of central origin. It is in precise inverse proportion to the intensity of the perturbation [11]. It remains constant in each individual for a given perturbation.

During this delay, the additional thermal load undergone by the subject may be given approximately by the expression $(H_2 - H_1)\ t$. Thus the body has necessarily gained heat, the stored quantity accumulated during this delay being S_d. This quantity is constant for a given individual no matter what the amplitude of the perturbation may be [32]. Since the weight and specific heat of the body may be considered constant, this storage process is necessarily translated (cf. equation 1) into an increase in body temperatures, the main increase occurring in T_{sk}. Physiologically, the result

is a quantative and qualitative change in the signals reaching the controller.

If steady state I was such that the body was already sweating (a T_a of 40°C, for example), then the delay is virtually zero [66, 59]. Finally, this delay may undergo a decrease under the effect of acclimatization. We have suggested this possibility elsewhere [12, 15] and it seems to have been demonstrated by the most recent work of Vogt [69] and Henane and Valatx [29].

Phase 2: This is the start of evaporation and a progressive increase in its rate until a new steady state $\dot{E}_2$ is reached. As has just been pointed out, evaporation begins when the stored heat S_d has reached a given level [32, 66] which is approximately constant for each subject, the average being on the order of 3 kJ/kg body weight. Thus there is a starting threshold which corresponds to "non-linearity" from a control theory standpoint.

The curve representing the rate of evaporation as a function of time assumes an exponential shape [12, 15, 67], as shown in Fig. 4. Although we have recently stated some reservations [59, 34], for purposes of simplification one may assume this curve to possess a single time constant τ.

During the time the rate of evaporation takes to reach its steady state level, there continues to be a given heat storage rate which gradually tends toward zero. At time t_2, the new steady state II is reached, but the integral of $\dot{S}$ between t_0 and t_2 will persist. This integral corresponds to a value S which is actually an increase /A325 in the quantity of body heat and which it is therefore preferable to write as ΔS.

From a physiological standpoint, it goes without saying that this value S is experienced by the body as a quantitative and qualitative variation in the signals generated by the thermoreceptors between the two steady states I and II. The mathematical integration of $\dot{S}$ is actually performed directly by these receptors, which

in all probability are more sensitive to the temperature itself than to its derivative.

At any rate, it necessarily follows that there is an increase in the body temperatures, i.e. T_{de} and T_{sk}. Taking into account the physical relationship described by Eq. (1), which links the difference in quantity of heat, here S, the temperature variation, here the average body temperature ΔT_b, body weight, and specific heat, it is possible to show [36] that S is a function of:

a) The thermal load levels corresponding to steady states I and II, that is, $\dot{H}_1$ and $\dot{H}_2$;

b) The time constant τ;

c) The quantity of heat stored during the delay, S_d.

Assuming the simplest mathematical case, that in which the delay is zero (cf. above), the equation is simplified to become:

$$S = (\dot{H}_2 - \dot{H}_1)\,\tau\left(1 - \exp\frac{t}{\tau}\right) - \dot{H}_1\,t \qquad (3)$$

in which $t = t_2 - t_1$.

Phase 3: Steady state II is reached. The net balance for the body is a stored quantity S defined by the above equation, to which the value S_d is added when a delay has occurred. S therefore depends solely on the quantity stored during the delay, $\dot{H}_1$, $\dot{H}_2$ and τ. The average body temperature, that is, the weighted sum of T_{de} and T_{sk}, with any given method of weighting, is increased by a given value ΔT_b which is a direct function of S. One can see that it is not necessary to draw on a random variation in a hypothetical reference temperature to explain this temperature increase, observed at both the central and peripheral levels.

This type of regulation is specifically defined in control theory: it is the regulation of heat exchange by a servomechanism. From a physiological standpoint, the entire process occurs as if the regulatory mechanism were acting on the heat storage rate $\dot{S}$, which corresponds to a gain or loss in heat for the body at each instant,

depending on whether it is positive or negative. This necessarily /A326
has an effect on the temperature of the thermodetectors of the body, and thus on the nature of the overall signal transmitted to the control centers. Thus the assumption of a specific, hypothetical temperature which is directly controlled by thermostat is replaced by the assumption that, from the weighted sum of all the signals it recieves, the heat controller is informed not only as to the rate of heat storage $\dot{S}$ by the phasic operation of its receptors, but also -- and probably especially -- as to the value S by the tonic operation of its receptors. Obviously this is only in the nature of a diagram, since the respective significance of these two modes of operation has yet to be defined with accuracy. These are actual experimental findings, however.

This concept offers the advantage of directly explaining the relationship between T_{de} and the thermal load, by giving it in mathematical form. Moreover, this is a modality which is completely defined by control theory.

An analog model has been developed from this concept. It has been formulated in Laplace transforms, as is current practice in control theory. It has then been programmed on an analog computer (EAI 580). The details of this program have been reported in a thesis by A. Sauvage [59].

V. ESTABLISHMENT OF MODEL

Since physiologists are not always familiar with the Laplace transfer and transformation equations, a purely physiological diagram will first be set up. Following this, a real model, equivalent to this diagram, will be constructed in accordance with control theory methodology.

A. Physiological Diagram

1) At a given instant DT, the algebraic sum of the instantaneous exchanges determines a given level of body heat. This summation

(equation 2) may be represented on the diagram by a "comparator" whose output will therefore be $\dot{S}$. This is a purely physical, passive summation, that is, one which involves no strictly physiological action. However, the heat gained or lost in this way is not distributed uniformly throughout the body. Schematically, one can use the classical expedient of assuming that the body is divided into two compartments: the center and the periphery. Let us assume the body to be undergoing positive storage ($\dot{S}$ 0). Be- /A327
tween a time t_1 and a time t_2, its center will have gained a given quantity of heat. Allowing for its weight and specific heat, the center will have undergone an increase in temperature to a given value. It is therefore possible to calculate a relationship, a transfer function, between T_{de} and $\dot{S}$. This relationship should reveal that the variation of T_{de} is a function of the stored heat, that is, the integral of $\dot{S}$. Figure 5 takes the first part of this reasoning into account. Except in regard to the center-periphery distribution coefficient, which is partly dependent on vasomotricity. it will be seen that the problem remains totally passive in nature. The level at which T_{de} stabilizes appears as the passive result of the variations in $\dot{S}$. Figure 5 gives a graphic representation of the passive instantaneous summation of thermal fluxes (cf. Equation 2) and the center-periphery distribution.

2) The same problem is also presented in regard to the relationship between T_{sk} and $\dot{S}$. This relationship is more complex at first glance, however, since the level of T_{sk} depends on the rate of heat storage, but more importantly, on the vasomotor phenomena which determine the transfer of heat from the center to the periphery. In addition, T_{sk} is one of the factors involved in the heat exchanges between the body and its environment. The exchanges by convection, conduction and radiation, previously defined as the external load, /A328
are known to be related to the temperature differential between the skin and the environment, according to a relationship which may be given in simplified form as:

$$H_{ext} = h(T_{sk} - T_a) \text{ per surface unit} \qquad (4)$$

in which h is a combined exchange coefficient (cf. [16]).

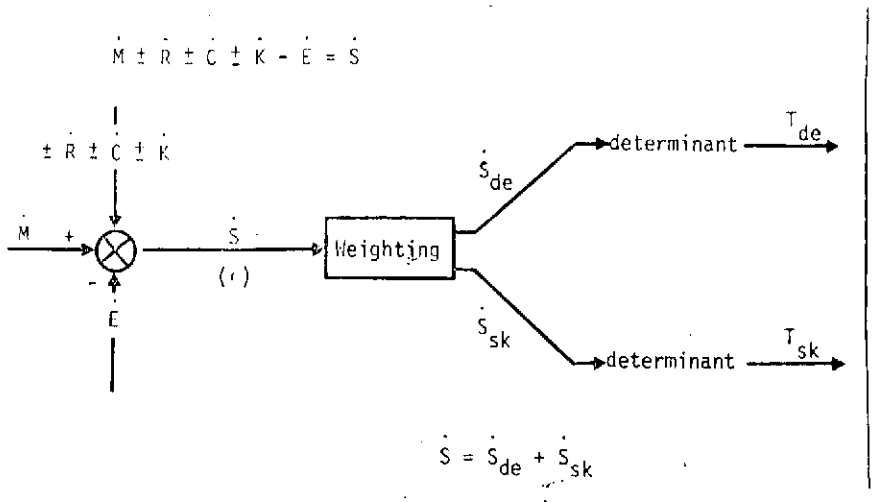

Fig. 5: Graphic representation of passive instantaneous summation of thermal fluxes (cf. Equation 2) and center-periphery distribution.

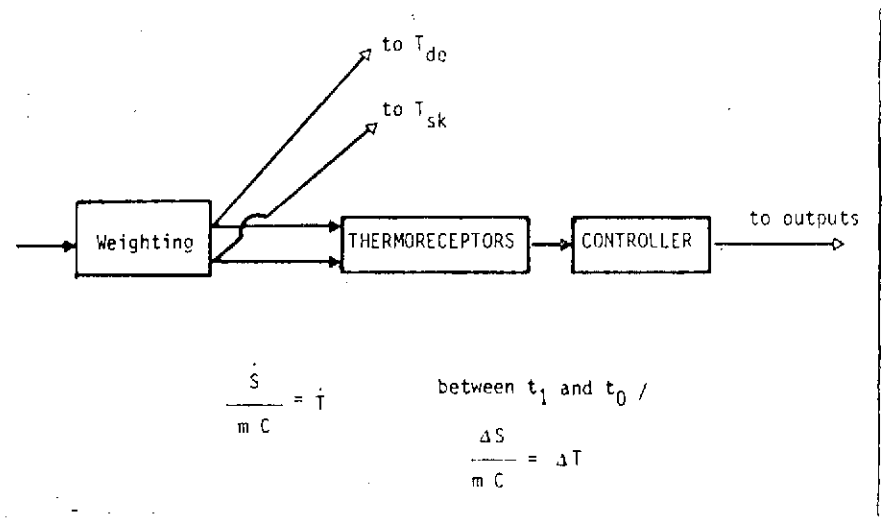

Fig. 6: Graphic representation of the relationship between S and T_{de} (as well as T_{sk}) and of the intervention of thermoreceptors (cf. text).

3) Furthermore, the effect of the increase in T_{de} and in T_{sk} between times t_0 and t_2 is to modify the signals generated by the thermoreceptors. The convergence of the signals on the heat controllers (Fig. 6) results in the involvement -- after a given latency period, if necessary -- of effector mechanisms: vasomotor

phenomena, followed by evaporation phenomena. Moreover, these two types of mechanisms do not occur on the same level and do not have the same quantitative significance. The vasomotor phenomena come into play primarily in center-periphery transfer. In this respect they are one of the factors in T_{sk}, and to a certain extent in the center-periphery distribution; secondarily, they are also a factor in T_{de} (Fig. 7).

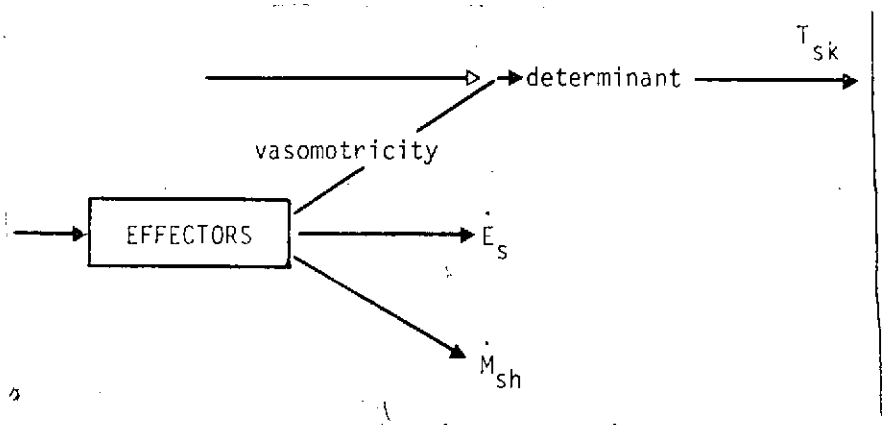

Fig. 7: T_{sk} determinants (cf. text).

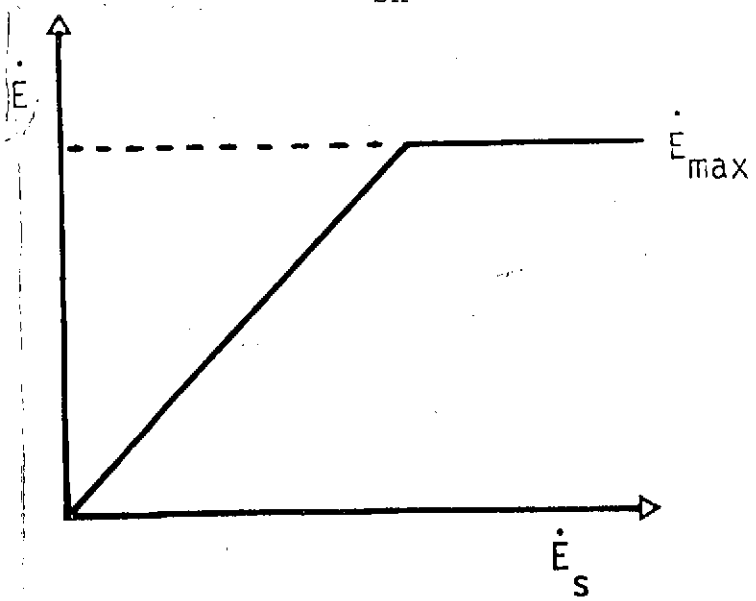

Fig. 8: Schematic representation of the involvement of the evaporativity of the environment as a factor limiting sweat evaporation.

4) The essential heat- /A329 combating mechanism in man is the evaporation of sweat, which, expressed in terms of heat flux, is represented as $\dot{E}_s$. Only the part of $\dot{E}_s$ which evaporates contributes to the loss of heat $\dot{E}$. Although the role of the /A330 environmental factors P_{wa} and V is relatively complex, to simplify, one may state that it will be possible for all the sweat to evaporate as long as $\dot{E}$ is less than the maximum heat evaporativity of the environment. If this is not the case, a limit will be reached. This phenomenon is represented by the graph given in Fig. 8.

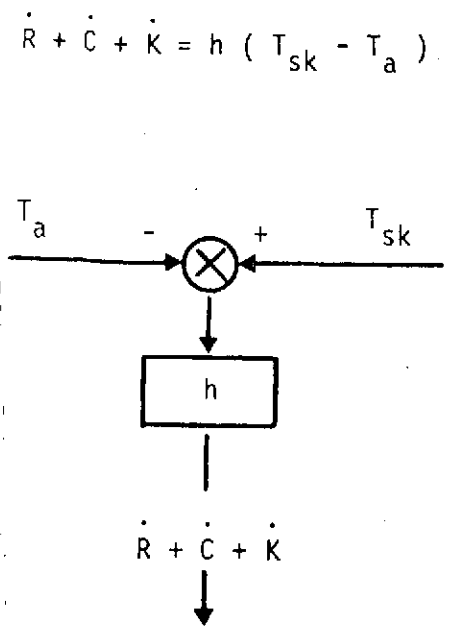

Fig. 9: Representation of exchanges by convection and radiation (exchanges by conduction being omitted) (cf. text).

Furthermore, $\dot{E}$ is looped, since it constitutes one of the modes of heat exchange (Fig. 5).

5) Finally, the diagram is completed by the existence of another loop, that of T_{sk}, which compared to T_a determines the magnitude of the exchanges by convection and radiation (Equation 4). Exchanges by conduction are overlooked since they are often extremely light under ordinary experimental conditions. (Fig. 9).

We have not dealt with cold-combating mechanisms in this model, since sufficiently precise data are not available in this area. However, it is fairly easy to conceive of the qualitative relationship between controller and effector, which here is the increase in metabolic heat flux due to shivering, $\dot{M}_{sh}$. This flux is added to the basal metabolic heat flux $\dot{M}_0$. The physiological diagram of this phenomenon is given by the graph in Fig. 10. /A331

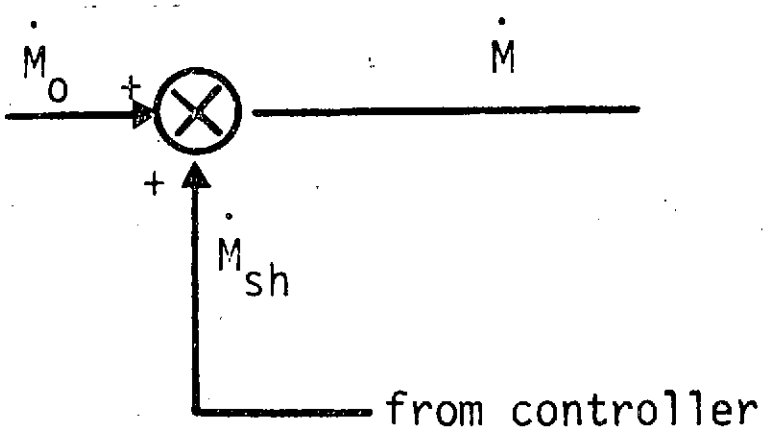

Fig. 10: Representation of the increase in thermal metabolism due to shivering during regulation in response to cold (cf. text).

Fig. 11 thus shows the overall physiological diagram.

However, this diagram cannot be used directly to construct an actual model, since it does not contain sufficiently precise physiological data in regard to certain transfer functions: /A332

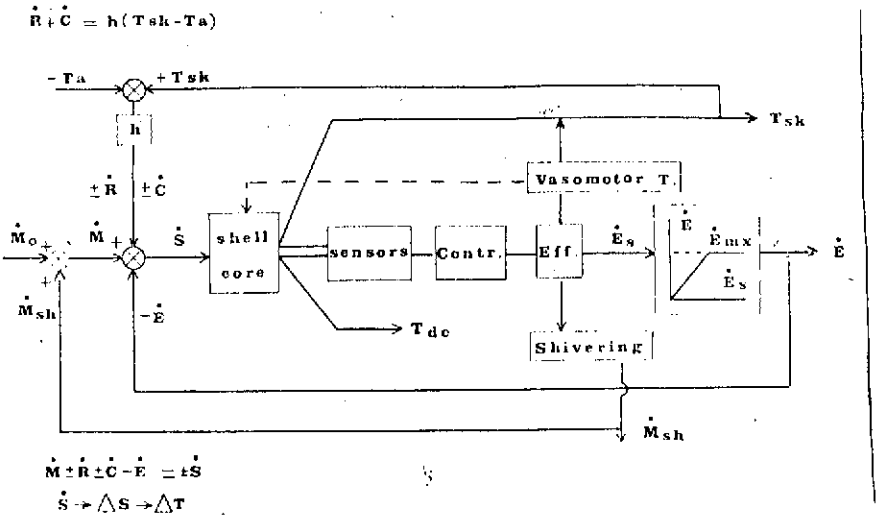

Fig. 11: Overall physiological diagram of indirect regulation of the central temperature, based on the theory of a servomechanism for heat exchange (cf. text).

the quantitative aspect of the thermoreceptors-controller relationship is unknown, for example. The quantitative model should therefore establish overall relationships, since the specific relationships are not known.

B. Quantitative Model

This model is exactly the same as the preceding, but the transfer functions are global. However, regulation in response to cold is not included, for the same reason (Fig. 10): because the literature furnishes no sufficiently precise data on the relationship between $\dot{M}_{sh}$ and $\dot{S}$. Finally, for purposes of graphic simplification, we have omitted the phenomenon illustrated by Fig. 8. Under our experimental conditions, which served as the basis of determination of the transfer equations, the evaporativity of the environment was always more than adequate.

1) On the basis of the experimental results given above, an overall transfer function was defined between $\dot{S}$ and $\dot{E}$. It therefore includes the different elements in Fig. 6: thermoreceptors, controller and effector. It was possible to place this function

in the second order [59, 36] and, as a Laplace transform, it is represented by a function of the following type:

$$\frac{k_E}{s(1 + \tau_E s)} \tag{5}$$

in which k_E is the overall gain of the system, τ_E the time constant of the equation and s the complex Laplace variable.[4] Since the Laplace transformation is an integration process, it clearly shows that $\dot{E}$ is related to the integral of $\dot{S}$; physiologically, this means that $\dot{E}$ is related to the weighted sum of the body temperatures.

2) In a similar manner, an attempt was made to determine a transfer function between $\dot{S}$ and T_{sk} on the basis of the data reported primarily in [30]. This function, which therefore includes the vasomotor phenomena among other factors, is of the type:

$$\frac{1}{1 + \tau_{sk} s} \tag{6}$$

in which τ_{sk} is the time constant. Furthermore, T_{sk} is looped after comparison with T_a according to Fig. 9.

3) Finally, the overall transfer function of the central temperature is somewhat simpler and is given by the expression: /A333

$$\frac{11}{m_{de} C s} \tag{7}$$

in which m_{de} is the mass of the center and C its specific heat. This expression shows that the final level of T_{de} is a function of the integral of $\dot{S}$, that is, the quantity of heat stored. More importantly, it also shows that, setting aside the effect of temperature on metabolism (Q_{10}), T_{de} is in an open loop. The central temperature is therefore regulated, but in an indirect manner, and its level of regulation does not depend on a set value of the central temperature, but on the way in which the body regulates $\dot{S}$,

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[4] The letter p is used by French control theorists to represent the complex Laplace variable, while American control theorists use the letter s.

allowing for its characteristics and especially the time constant of sweatyevaporation. Fig. 12 shows the overall model in its "control theory" form, as it has been programmed on an analog computer.

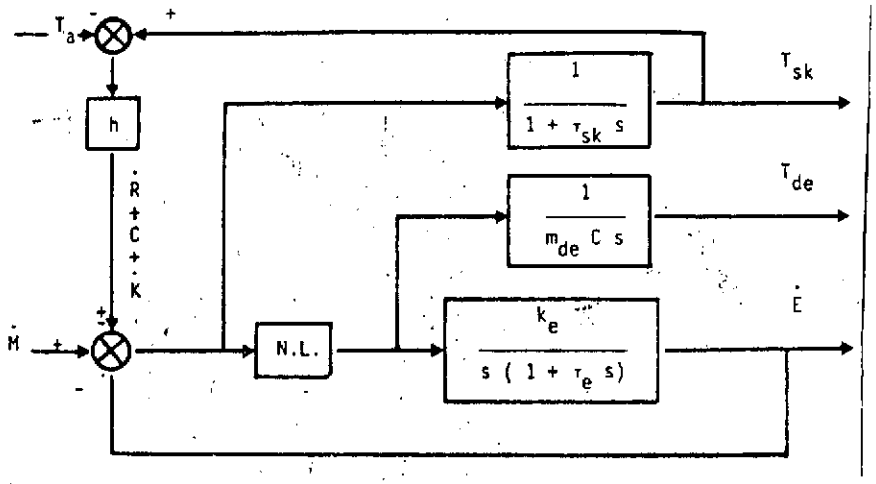

Fig. 12: Block diagram of thermoregulation model based on the theory of a heat exchange servomechanism (cf. text).

The numerical values of the mechanical parameters and the results of simulation are given in the Sauvage thesis [59] and in another of our reports which deals more specifically with the physics of this problem [36].

VI. DISCUSSION AND CONCLUSION /A334

The model presented here seems to be relatively simple. However, as was shown in the introduction to this article, the purpose of the preparation of this model was to determine the nature of the mechanism by which the body keeps its temperatures relatively constant. This model was also intended to be quantitative to permit simulation by computer. The basic conclusion which emerges is that, after thermal perturbation, the body does not seek to return itscentral temperature to a set point, either variable or non-variable (temperature regulation). Instead it seeks to return its instantaneous heat storage rate to zero as soon as possible: this

is an exchange servomechanism. The thermoreceptors, of course, do inform the controller as to the heat storage rate. But the final internal temperature level appears to be the result of the characteristics of the system as a whole, especially its response ratio (delay) and its overall time constant, whose determination is highly complex.

By the use of control theory methodology, we have merely wished to demonstrate the physical validity of this conceptualization. In comparison to the theory of direct regulation of T_{de}, it offers the advantage of requiring no additional assumptions, either on the determination of the regulated temperature or on the existence of a reference temperature, which moreover would be variable. This is because the initial "basal" state, that is, in regard to the internal temperature and average value of 37°C, is determined only passively, by the heat exchange laws of physics. The internal temperature of an inanimate object with the same heat transmission characteristics and surface characteristics as the human body, producing the same heat flux of 45 w/m^2, would stabilize at 37°C if the body were placed in a 30°C environment, without the involvement of any regulatory system. If, for purposes of clarity, one actually tries to define a set point, one finds that the thermal metabolism of the body is the very biological factor which may be considered to be the principle input of the system, environmental conditions being a secondary input. Physiologists concerned with the protection of the human body from heat by clothing are well aware that the best means of protecting a subject from an extremely inimical environment -- although this is hardly possible technically at the present time -- would be to heat-insulate the environment completely and to limit further procedures to the removal of the heat produced by metabolism, by suitable climate control.

The model presented also makes it possible to explain and simulate the experimental phenomena classically observed beyond the limits of normal physiology. If, for example, sweat evaporation is prevented, a technique which is frequently used in obtaining hyperthermic states, the model clearly shows that $\dot{S}$ will become

positive. As a result, T_{de} will undergo a passive increase. Furthermore, the controller will have a tendency to increase the sweat rate to no purpose; the system will reach a steady state only if one of the parameters, T_a, for example, is modified. This is what actually occurs in controlled hypothermia techniques [29].

An explanation for febrile hyperthermia, another example, may be drawn directly from the characteristics of this model, although it first must be complimented, of course, by the introduction of the effector "metabolic heat output due to shivering," as it has been presented above (Fig. 10). It suffices to assume that the pyrogenic agents change the gain of the controller, rather than the hypothetical reference temperature. This theory is plausible from the standpoint of control theory, and on a physiological level, it is one which has been put forth by other investigators [43]. In this case, the transfer function between $\dot{S}$ and $\dot{M}_{sh}$, which is still undetermined at present, is the factor which will be modified at a given instant. $\dot{M}$ will therefore increase, resulting in an increase in $\dot{S}$, followed by T_{de}. A steady state will be established, but T_{de} will continue to be increased by a given value until the change has stopped.

It therefore appears that the theory in which the thermal controller of the body is considered to be a thermostat may be replaced by another theory which provides a simpler explanation for the physiological phenomena observed, without the need for any additional assumptions: the controller acts as a servomechanism for the rate of heat storage by the body, that is, the instantaneous sum of the thermal exchange fluxes of the body. As a result, the temperatures of the various organs normally vary within an extremely narrow range.

REFERENCES

1. Abrams R., Hammel, H. T., "Cyclic variations in hypothalamic temperature in unanesthetized rats," Am. J. Physiol. 208, 698-702 (1965).

2. Adolph, E. F., "The initiation of sweating in response to heat," Am. J. Physiol., 145, 710-715 (1946).

3. Baker, M. A., Hayward, J. N., "Automatic basis for the rise in brain temperature during paradoxical sleep," Science 157, 1586-1588 (1967).

4. Benzinger, T. H.,"Heat regulation: homeostasis of central temperature in man," Physiol. Rev. 49, 671-759 (1969).

5. Benzinger, T. H., Kitzinger,=C., Pratt, A. W., "The human thermostat," in J. D. Hardy, Temperature: its measurement and control in science and industry 3(part 3), 637-655, Reinhold Pub. Co., New York (1963).

6. Birzis L., Hemingway, A., "Efferent brain discharges during shivering," J. Neurophysiol., 20, 156-163 (1957).

7. Bonaventure, M., Ginestet, A., Houdas, C., Sauvage, A., Houdas, Y., "Modification of the evaporative heat losses during a rapid rise in ambient humidity," Paper presented at the 25th Conference on Physiology, Besancon, 1972.

8. Bullard, R.,W., Banerjee, M. R., McIntyre, B. A., "The role of the skin in negative feedback regulation of eccrine sweating," Int. J. Biometeorol. 11, 93-104 (1967).

9. Chatonnet, J., Tanche, M., "Dissociation of "central" shivering and "reflex" shiver in the dog with destroyed spinal chord," J. Physiol. 48, 439-442, Paris (1956).

10. Chatonnet, J., Tanche, M., "Arguments in favor of central regulation of thermogenesis in the dog," Symposium on Temperature Regulation, Bad-Nauheim, 1956.

11. Colin, J., Boutelier, C., Houdas, Y., "The effect of thermal load on thermal sweating initiation time in man," J. Pysiol. 58, 217-218, Paris (1966).

12. Colin, J., Houdas, Y., "Initiation of sweating after abrupt rise in environmental temperature," J. Appl. Physiol. 20, 984-990 (1965).

13. Colin, J., Houdas, Y., "Respective influence of peripheral and central detectors in the initiation of thermal sweating in man," J. Physiol. 57, 234-235, Paris (1965).

14. Colin, J., Houdas, Y., "The mean temperature concept in study of the initiation of thermal sweating," C. R. Soc. Biol. 160, 2076-2078 (1966).

15. Colin, J., Houdas, Y., "Determining factors in thermal sweating in man," J. Physiol. 60, 5-31, Paris, (1968).

16. Colin, J., Timbai, J., Boutelier, C., Guieu, J. D., Houdas, Y., "Combined effect of radiation and convection," in J. D. Hardy et al., Physiological and behavioural temperature regulation, Thomas, Springfield, Ill., 81-96, 1970.

17. Craig, A. B., Dvorak, M., "Thermal regulation during water immersion," J. Appl. Physiol., 21, 1577-1585 (1966).

18. Crosbie, R. J., Hardy, J. D., Fessenden, E., "Electrical analog simulation of temperature regulation in man," in J. D. Hardy, Temperature: its measurement and control in science and industry 3 (part 3), Rheinhold Pub., Co., New York, 627-635, (1963.

19. Elizondo, R. S., Bullard, R. W., "Local determinants of sweating and the assessment of set-point," Int. J. Biometeorol. 15, 273-280 (1971).

20. Gee, G. K., Goldman, R. F., "Heat loss of man in total water immersion," 24th ann. Fall Meeting (Am. Physiol. Soc.), Rochester, N. Y., 1973.

21. Gille, J. C., Decaulne, P., Pelegrin, M., Dynamique de la commande linéaire [The Dynamics of Linear Control], Vol. 1, p. 475, Dunod, Paris, 1967.

22. Glaser, E. M., Newling, P. S. B., "The control of body temperature in thermal balance," J. Physiol. 137, 1-11, London (1957).

23. Guieu, J. D., Hardy, J. D., "Effects of heating and cooling of the spinal cord on preoptic unit activity," J. Appl. Physiol. 29, 675-683 (1970).

24. Hammel, H. T., Jackson, D. C., Stolwijk, J. A. J., Hardy, J. D., Stromme, S. B., "Temperature regulation by hypothalamic proportional control with an adjustable set point," J. Appl. Physiol. 18, 1146-1154 (1963).

25. Hardy, J. D., "Central and peripheral factors in physiological temperature regulation" in Les concepts de C. Bernard sur le milieu intérieur [The concepts of C. Bernard on the internal environment], Masson, Paris, 247-283, 1967.

26. Hardy, J. D., "Models of temperature regulation: A review," in J. Bligh and R. Moore, Essays on temperature regulation, North-Holland Pub. Co., Amsterdam, p. 162-186, 1972.

27. Heerd, E., Behmann, F. W., Heinrichs, H. J., "The relationship of human thermal sweating to cutaneous and rectal temperature," Pflügers Arch. 266, 52, (1957).

28. Hellon, R. F., "Thermal stimulation of hypothalamic neurons in unanesthetized rabbits," J. Physiol. 193, 381-395, London, (1967).

29. Henane, R., Valatx, J. L., "Thermoregulatory changes induced during heat acclimatization by controlled hyperthermia in man," J. Physiol. 230, 255-271, London (1973).

30. Houdas, Y., Colin, J., Timbal, J., Boutelier, C., Guieu, J. D., "Skin temperatures in warm environments and the control of sweat evaporation," J. Appl. Physiol. 33, 99-104 (1972).

31. Houdas, Y., Delabre, M., "Determination of a servo diagram for human thermoregulatory mechanisms in response to heat," J. Physiol. 61, (suppl. 2), p1 319, Paris (1969).

32. Houdas, Y., Sauvage, A., "Servomechanism of heat loss in man subjected to an external heat load," C. R. Ac. Sci. 273 (Series D), 2294-2297 (1971).

33. Houdas, Y., Sauvage, A., "The response of the human thermostat to an input gradient of the external thermal load J. Physiol. 63, 279-281, Paris (1971).

34. Houdas, Y., Sauvage, A., Bonaventure, M., Guieu, J. D., "Model of the evaporative response to thermal load increase," J. Physiol 66, 137-161, Paris (1973).

35. Houdas, Y., Sauvage, A., Bonaventure, M., Guieu, J. D., "Control of heat exchanges: an alternate concept for temperature regulation," in A. S. Iberall and A. C. Guyton, Regulation and control in physiological systems, Int. Fed. Autom. Control. Pub., Pittsburgh, p. 217-220, 1973.

36. Houdas, Y., Sauvage, A., Bonaventure, M., Ledru, C., Guieu, J. D., "Thermal control in man: regulation of central temperature or adjustment of heat exchanges by servomechanism?," J. Dyn. Syst. (ASME Trans.) 95, (Series G), 331-335 (1973).

37. Huckaba, C. E., Downey, J. A., "Overview on human thermoregulation," in A. S. Iberall and A. C. Guyton Regulation and control in physiological systems, Int. Fed. Autom. Control, Pub., Pittsburg, pp. 212-216, 1973.

38. Kastella, K. G., Brown, A. C., "Effects of hypothalamic temperature waveforms on peripheral blood flow in the baboon," J. Appl. Physiol. 29, 499-507 (1970)

39. Kawamura, H., Sawyer, C., "Elevation in brain temperature during paradoxical sleep," Science 150, 912-913 (1965).

40. Ledru, C., Bonaventure, M., Lecroart, J. L., Guieu, J. D., Houdas, Y., "Frequency response of the human thermoregulatory system," J. Physiol 67, p. 228A, Paris (1973).

41. Lipton, J. M., "Thermosensitivity of medulla oblongata in control of body temperature," Am. J. Physiol. 224, 890-897 (1973).

42. Milhorn, H., T., The application of control theory to physiological systems, Vol. 1, W. B. Saunders, Philadelphia, p. 386, 1966.

43. Mitchell,DD., Snellen, J. W., Atkins, A. R., "Thermoregulation during fever: change of set-point or change of gain?," Pflügers Arch. 321, 293-302 (1970).

44. Nadel, E. R., Bullard, R. W., Stolwijk, J. A. J., "Importance of skin temperature in the regulation of sweating," J. Appl. Physiol. 31, 80-87 (1971).

45. Nadel, E. R., Mitchell, J. W., Saltin, B., Stolwijk, J. A. J., "Peripheral modifications to the central drive for sweating," J. Appl. Physiol. 31, 828-833 (1971).

46. Nakayama, T., Hardy, J. D., "Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature," J. Sppl. Physiol. 27, 848-857 (1969).

47. Nielsen, B., "Thermoregulation in rest and exercise," Acta physiol. scand. 76 (suppl. 323), 1-74 (1969).

48. Nielsen, M., "Regulation of body temperature during muscular work," Skand, Arch. Physiol. 79, 193-230 (1938).

49. Nutik, S. L., "Effect of temperature change of the preoptic region and skin on posterion hypothalamic neurons," J. Physiol. 63, 368-370, Paris (1971)

50. Parmeggiani, L., Franzini, C., Lenzi, P., Cianci, T., "Inguinal subcutaneous temperature changes in cat sleeping at different environmental temperatures," Brain Res. 33, 397-404 (1971).

51. Randall, W. C., Rawson, R. O., McCook, R. D., Peiss, C. N., "Central and peripheral factors in dynamic thermoregulation," J. Appl. Physiol. 18, 61-64 (19163).

52. Rawson, R. O, Quick, K. P., "Evidence of deep body thermoreceptor response to intraabdominal heating in the ewe," J. Appl, Physiol. 28, 813-820 (1970).

53. Rawson, R. O., Stolwijk, J. A. J., Graichen, H., Abrams, R., "Continuous radiotelemetry of hypothalamic temperature from unrestrained animals," J. Appl. Physiol. 20, 321-325, (1965).

54. Richet, C., "Heat" in Dictionary of Physiology, 3, Alcan, Paris, pp. 81-274, 1898.

55. Saltin, B., Gagge, A. P., Bergh, U., Stolwijk, J. A. J., "Body temperatures and sweating during exhaustive exercise," J. Appl. Physiol. 32, 635-643 (1972).

56. Saltin, B., Gagge, A. P., Stolwijk, J. A. J., "Body temperatures during submaximal exercise in man," J. Appl, Physiol. 25, 679-688 (1968).

57. Saltin, B., Gagge, A. P., Stolwijk, J. A. J., "Body temperatures and sweating during thermal transients caused by exercise," J. Appl. Physiol. 28, 318-327 (1970).

58. Saltin, B., Hermansen, L., "Esophageal, rectal and muscle temperatures during exercise," J. Appl. Physiol. 21, 1757-1762 (1966).

59. Sauvage, A., Thermoregulatory system: A model of heat loss in man subjected to an external thermal load, Doctoral Thesis in Engineering (Control Theory), Lille, p. 126, 1972.

60. Simon, e., "The role of the spinal cord in thermoregulation," Arch. Sci. Physiol. 21, 215-233 (1967).

61. Snellen, J. W., "Mean body temperature and the control of thermal sweating," Acta Physiol. neerl. 14, 99-174,(1966).

62. Snellen, J. W., "Set-point in exercise," in J. Bligh and R. Moore, Essays on temperature regulation, North-Holland, Pub. Co., Amsterdam, pp. 140-148, 1972.

63. Stolwijk, J. A. J., "A mathematical model on physiological temperature regulation in man," NASA Rep. C. R., 1885, 1971.

64. Stolwijk, J. A. J., Nadel, E. R., "Sweating response in human thermoregulation," in A. S. Iberall and A. C. Guyton, Regulation and control in physiological systems, Int. Fed. Autom. Control. Pub., Pittsburgh, pp. 221-223, 1973.

65. Stolwijk, J. A. J., Nadel, E. R., Mitchell, J. W., Saltin, B., "Modification of central sweating drive at the periphery," Int. J. Biometeorol. 15, 268-272 (1971).

66. Timbal, J., "Study of sweating after an abrupt rise in ambient temperature, Thesis in Human Biology, Lille, p. 174, 1971.

67. Timbal, J., Colin, J., Guieu, J. D., Boutelier, C., "A mathematical study of thermal losses by sweating in man," J. Appl. Physiol. 27, 726-730, (1968).

68. Valatx, J. L., Roussel, B., Cure, M., "Sleep and cerebral temperature of the rat during chronic exposure to a hot environment," Brain Res. 55, 107-122 (1973).

69. Vogt, J. J., "Effect of repeated exposure to hot environment on the initiation of sweating by stepped ambient temperature increases in man," J. Physiol. 58, Paris, p. 737 (1966).

70. Wit, A., Wang, S. C., "Temperature-sensitive neurons in preoptic/anterior hypothalamic region: effects of increasing ambient temperature Am. J. Physiol. 215, 1160-1169 (1968).

71. Woodcock, A. H., Breckenridge, J. R., "A model description of thermal exchange for the nude man in hot environments," Ergonomics 8, 223-235 (1965).

72. Wunnenberg, W., Hardy, J. D., "Response of single units of the po posterior hypothalamus to thermal stimulation," J. Appl. Physiol. 33, 547-552 (1972).